

1. NAME OF THE MEDICINAL PRODUCT

Veoza 45 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 45 mg of fezolinetant.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Round, light red tablets (approximately 7 mm diameter × 3 mm thickness), debossed with the company logo and '645' on the same side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Veoza is indicated for the treatment of moderate to severe vasomotor symptoms (VMS) associated with menopause (see section 5.1).

4.2 Posology and method of administration

Posology

The recommended dose is 45 mg once daily.

Benefit of long-term treatment should be periodically assessed since the duration of VMS can vary by individual.

Missed dose

If a dose of Veoza is missed or not taken at the usual time, the missed dose should be taken as soon as possible, unless there is less than 12 hours before the next scheduled dose. Individuals should return to the regular schedule the following day.

Special populations

Elderly

Fezolinetant has not been studied for safety and efficacy in women initiating Veoza treatment over 65 years of age. No dose recommendation can be made for this population.

Hepatic impairment

No dose modification is recommended for individuals with Child-Pugh Class A (mild) chronic hepatic impairment (see section 5.2).

Veoza is not recommended for use in individuals with Child-Pugh Class B (moderate) or C (severe) chronic hepatic impairment. Fezolinetant has not been studied in individuals with Child-Pugh Class C (severe) chronic hepatic impairment (see section 5.2).

Renal impairment

No dose modification is recommended for individuals with mild (eGFR 60 to less than 90 ml/min/1.73 m²) or moderate (eGFR 30 to less than 60 ml/min/1.73 m²) renal impairment (see section 5.2).

Veozza is not recommended for use in individuals with severe (eGFR less than 30 ml/min/1.73 m²) renal impairment. Fezolinetant has not been studied in individuals with end-stage renal disease (eGFR less than 15 ml/min/1.73 m²) and is not recommended for use in this population (see section 5.2).

Paediatric population

There is no relevant use of Veozza in the paediatric population for the indication of moderate to severe VMS associated with menopause.

Method of administration

Veozza should be administered orally once daily at about the same time each day with or without food and taken with liquids. Tablets are to be swallowed whole and not broken, crushed, or chewed due to the absence of clinical data under these conditions.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Concomitant use of moderate or strong CYP1A2 inhibitors (see section 4.5).

Known or suspected pregnancy (see section 4.6).

4.4 Special warnings and precautions for use

Medical examination/consultation

Prior to the initiation or reinstatement of Veozza, a careful diagnosis should be made, and complete medical history (including family history) must be taken. During treatment, periodic check-ups must be carried out according to standard clinical practice.

Liver disease

Veozza is not recommended for use in individuals with Child-Pugh Class B (moderate) or C (severe) chronic hepatic impairment. Women with active liver disease or Child-Pugh Class B (moderate) or C (severe) chronic hepatic impairment have not been included in the clinical efficacy and safety studies with fezolinetant (see section 4.2) and this information cannot be reliably extrapolated. The pharmacokinetics of fezolinetant has been studied in women with Child-Pugh Class A (mild) and B (moderate) chronic hepatic impairment (see section 5.2).

Hepatotoxicity

Elevations in serum alanine aminotransferase (ALT) levels at least 3 times the upper limit of normal (ULN) occurred in 2.1% of women receiving fezolinetant compared to 0.8% of women receiving placebo. Elevations in serum aspartate aminotransferase (AST) levels at least 3 times the ULN occurred in 1.0% of women receiving fezolinetant compared to 0.4% of women receiving placebo (see section 4.8). ALT and/or AST elevations were not accompanied by an increase in bilirubin (greater than two times the ULN, i.e., there were no cases of Hy's law) with fezolinetant. Women with ALT or AST elevations were generally asymptomatic. Transaminase levels returned to pre-treatment levels (or close to these) without sequelae with dose continuation, and upon dose interruption, or discontinuation.

In the post-marketing setting, cases of serious but reversible hepatotoxicity have been reported within the first few weeks of treatment. Patients have experienced transaminase elevations (greater than 10 times the ULN) with concurrent elevations in bilirubin and/or alkaline phosphatase (ALP), sometimes associated with signs or symptoms such as fatigue, pruritus, jaundice, dark urine, or abdominal pain.

Evaluate hepatic function (ALT, AST, ALP, and bilirubin) before initiating therapy. Do not initiate fezolinetant if ALT or AST is equal to or exceeds 2 times the ULN or if the total bilirubin is elevated (e.g., equal to or exceeds 2 times the ULN).

Patients should discontinue fezolinetant immediately and seek medical attention, including hepatic laboratory tests, if they experience signs or symptoms that may suggest hepatotoxicity such as new onset fatigue, decreased appetite, nausea, vomiting, pruritus, jaundice, pale faeces, dark urine, or abdominal pain.

Follow-up evaluation of hepatic function is recommended monthly for the first three months of initiating fezolinetant and thereafter periodically based on clinical judgement.

Discontinue fezolinetant if:

- transaminase elevations are greater than 5 times the ULN.
- transaminase elevations are greater than 3 times the ULN and the total bilirubin level is greater than 2 times the ULN.

Exclude alternative causes of hepatic laboratory test elevations.

Known or previous breast cancer or oestrogen-dependent malignancies

Women undergoing oncologic treatment (e.g., chemotherapy, radiation therapy, anti-hormone therapy) for breast cancer or other oestrogen-dependent malignancies have not been included in the clinical studies. Therefore, Veoza is not recommended for use in this population as the safety and efficacy are unknown.

Women with previous breast cancer or other oestrogen-dependent malignancies and no longer on any oncologic treatment have not been included in the clinical studies. A decision to treat these women with Veoza should be based on a benefit-risk consideration for the individual.

Concomitant use of hormone replacement therapy with oestrogens (local vaginal preparations excluded)

Concomitant use of fezolinetant and hormone replacement therapy with oestrogens has not been studied, and therefore concomitant use is not recommended.

Seizures or other convulsive disorders

Fezolinetant has not been studied in women with a history of seizures or other convulsive disorders. There were no cases of seizures or convulsive disorders during clinical studies. A decision to treat these women with Veoza should be based on a benefit-risk consideration for the individual.

4.5 Interaction with other medicinal products and other forms of interaction

Effect of other medicinal products on fezolinetant

CYP1A2 inhibitors

Fezolinetant is primarily metabolised by CYP1A2 and to a lesser extent by CYP2C9 and CYP2C19. Concomitant use of fezolinetant with medicinal products that are moderate or strong inhibitors of CYP1A2 (e.g., ethinyl oestradiol containing contraceptives, mexiletine, enoxacin, fluvoxamine) increase the plasma C_{max} and AUC of fezolinetant.

Concomitant use of moderate or strong CYP1A2 inhibitors with Veoza is contraindicated (see section 4.3).

Co-administration with fluvoxamine, a strong CYP1A2 inhibitor, resulted in an overall 1.8-fold increase in fezolinetant C_{max} and 9.4-fold increase in AUC; no change in t_{max} was observed. Given the large effect of a strong CYP1A2 inhibitor and supportive modelling, the increase in fezolinetant concentrations is expected to be of clinical concern also following concomitant use with moderate CYP1A2 inhibitors (see section 4.3). The increase in fezolinetant exposure was however not predicted to be clinically relevant following concomitant use with weak CYP1A2 inhibitors.

CYP1A2 inducers

In vivo data

Smoking (moderate inducer of CYP1A2) decreased fezolinetant C_{max} to a geometric LS mean ratio of 71.74%, while AUC decreased to a geometric LS mean ratio of 48.29%. No significant difference in efficacy was observed between smokers and non-smokers. No dose modification is recommended for smokers.

Transporters

In vitro data

Fezolinetant is not a substrate of P-glycoprotein (P-gp). Major metabolite ES259564 is a substrate of P-gp.

Effect of fezolinetant on other medicinal products

Cytochrome P450 (CYP) enzymes

In vitro data

Fezolinetant and ES259564 are not inhibitors of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. Fezolinetant and ES259564 are not inducers of CYP1A2, CYP2B6, and CYP3A4.

Transporters

In vitro data

Fezolinetant and ES259564 are not inhibitors of P-gp, BCRP, OATP1B1, OATP1B3, OCT2, MATE1, and MATE2-K ($IC_{50} > 70 \mu\text{mol/l}$). Fezolinetant inhibited OAT1 and OAT3 with IC_{50} values of $18.9 \mu\text{mol/l}$ ($30 \times C_{max,u}$) and $27.5 \mu\text{mol/l}$ ($44 \times C_{max,u}$), respectively. ES259564 does not inhibit OAT1 and OAT3 ($IC_{50} > 70 \mu\text{mol/l}$).

4.6 Fertility, pregnancy and lactation

Pregnancy

Veozza is contraindicated during pregnancy (see section 4.3). If pregnancy occurs during use with Veozza, treatment should be withdrawn immediately.

There are no or limited data from the use of fezolinetant in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Perimenopausal women of childbearing potential should use effective contraception. Non-hormonal contraceptives are recommended for this population.

Breast-feeding

Veozza is not indicated during lactation.

It is unknown whether fezolinetant and its metabolites are excreted in human milk. Available pharmacokinetic data in animals showed excretion of fezolinetant and/or its metabolites in animal milk (see section 5.3). A risk to the suckling child cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Veozza therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

There are no data on the effect of fezolinetant on human fertility. In the fertility study in female rats, fezolinetant did not affect fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Fezolinetant has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The most frequent adverse reactions with fezolinetant 45 mg were diarrhoea (3.2%) and insomnia (3.0%).

There were no serious adverse reactions reported at an incidence greater than 1% across the total study population. On fezolinetant 45 mg, four serious adverse reactions were reported. The most serious adverse reaction was an event of endometrial adenocarcinoma (0.1%).

The most frequent adverse reactions leading to dose discontinuation with fezolinetant 45 mg were alanine aminotransferase (ALT) increased (0.3%) and insomnia (0.2%).

Tabulated list of adverse reactions

The safety of fezolinetant has been studied in 2203 women with VMS associated with menopause receiving fezolinetant once daily in phase 3 clinical studies.

Adverse reactions observed during clinical studies and from spontaneous reporting are listed below by frequency category in each system organ class. Frequency categories are defined as follows: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1\ 000$ to $< 1/100$); rare ($\geq 1/10\ 000$ to $< 1/1\ 000$); very rare ($< 1/10\ 000$); and not known (cannot be estimated from the available data).

Table 1. Adverse reactions for fezolinetant 45 mg

MedDRA system organ class (SOC)	Frequency category	Adverse reaction
Psychiatric disorders	Common	Insomnia
Gastrointestinal disorders	Common	Diarrhoea, Abdominal pain
Hepatobiliary disorders	Common	Alanine aminotransferase (ALT) increased, Aspartate aminotransferase (AST) increased
	Not known ¹	Hepatotoxicity ²

Preferred term in MedDRA (v.23.0).

¹ Adverse reactions of an unknown frequency have been identified during post-approval use of fezolinetant. Because these reactions were reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate the frequency or establish a causal relationship to drug exposure.

² See Description of selected adverse reactions section.

Description of selected adverse reactions

Hepatotoxicity

Serious cases of hepatotoxicity in which ALT and/or AST elevations were accompanied by an increase in total bilirubin including symptoms have been reported post-marketing (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

4.9 Overdose

Doses of fezolinetant up to 900 mg have been tested in clinical studies in healthy women. At 900 mg, headache, nausea, and paraesthesia were observed.

In the case of overdose, the individual should be closely monitored, and supportive treatment should be considered based on signs and symptoms.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other gynaecologicals, other gynaecologicals, ATC code: G02CX06.

Mechanism of action

Fezolinetant is a non-hormonal selective neurokinin 3 (NK3) receptor antagonist. It blocks neurokinin B (NKB) binding on the kisspeptin/neurokinin B/dynorphin (KNDy) neuron, which is postulated to restore the balance in KNDy neuronal activity in the thermoregulatory centre of the hypothalamus.

Pharmacodynamic effects

In postmenopausal women, with fezolinetant treatment, a transient decrease of luteinizing hormone (LH) levels was observed. No clear trends or clinically relevant changes in sex hormones measured (follicle-stimulating hormone (FSH), testosterone, oestrogen, and dehydroepiandrosterone sulphate) in postmenopausal women were observed.

Clinical efficacy and safety

Efficacy: Effects on VMS

The effects of fezolinetant were studied in postmenopausal women with moderate to severe VMS in two 12-week, randomised, placebo-controlled, double-blind phase 3 studies of identical design, followed by a 40-week extension treatment period (SKYLIGHT 1 – 2693-CL-0301 and SKYLIGHT 2 – 2693-CL-0302). Women who had a minimum average of 7 moderate to severe VMS per day were enrolled in the studies.

The study population included postmenopausal women defined as having amenorrhoea for ≥ 12 consecutive months (70.1%) or amenorrhoea for ≥ 6 months with FSH > 40 IU/l (4.1%) or having had bilateral oophorectomy ≥ 6 weeks prior to the screening visit (16.1%).

The study population included postmenopausal women with one or more of the following: prior hormone replacement therapy (HRT) use (19.9%), prior oophorectomy (21.6%), or prior hysterectomy (32.1%).

In the studies, a total of 1022 postmenopausal women (81% Caucasian, 17% Black, 1% Asian, 24% Hispanic/Latina ethnicity, and aged ≥ 40 years and ≤ 65 years with an average age of 54 years) were randomised and stratified by smoking status (17% smokers).

The 4 co-primary efficacy endpoints for both studies were the change from baseline in moderate to severe VMS frequency and severity to weeks 4 and 12 as defined in the Food and Drug Administration (FDA) and European Medicines Agency (EMA) guidelines. Each study demonstrated a statistically significant and clinically meaningful (≥ 2 hot flashes per 24 hours) reduction from baseline in the frequency of moderate to severe VMS to weeks 4 and 12 for fezolinetant 45 mg compared to placebo. Data from the studies showed a statistically significant reduction from baseline in the severity of moderate to severe VMS to weeks 4 and 12 for fezolinetant 45 mg compared to placebo.

Results of the co-primary endpoint for change from baseline to weeks 4 and 12 in mean frequency of moderate to severe VMS per 24 hours from SKYLIGHT 1 and 2 and from pooled studies are shown in Table 2.

Table 2. Mean baseline and change from baseline to weeks 4 and 12 for mean frequency of moderate to severe VMS per 24 hours

Parameter	SKYLIGHT 1		SKYLIGHT 2		Pooled studies (SKYLIGHT 1 and 2)	
	Fezolinetant 45 mg (n=174)	Placebo (n=175)	Fezolinetant 45 mg (n=167)	Placebo (n=167)	Fezolinetant 45 mg (n=341)	Placebo (n=342)
Baseline						
Mean (SD)	10.44 (3.92)	10.51 (3.79)	11.79 (8.26)	11.59 (5.02)	11.10 (6.45)	11.04 (4.46)
Change from baseline to week 4						
LS Mean (SE)	-5.39 (0.30)	-3.32 (0.29)	-6.26 (0.33)	-3.72 (0.33)	-5.79 (0.23)	-3.51 (0.22)
Mean % Reduction ²	50.63%	30.46%	55.16%	33.60%	52.84%	31.96%
Difference vs Placebo (SE)	-2.07 (0.42)	--	-2.55 (0.46)	--	-2.28 (0.32)	--
P-value	< 0.001 ¹	--	< 0.001 ¹	--	< 0.001	--
Change from baseline to week 12						
LS Mean (SE)	-6.44 (0.31)	-3.90 (0.31)	-7.50 (0.39)	-4.97 (0.39)	-6.94 (0.25)	-4.43 (0.25)
Mean % Reduction ²	61.35%	34.97%	64.27%	45.35%	62.80%	40.18%
Difference vs Placebo (SE)	-2.55 (0.43)	--	-2.53 (0.55)	--	-2.51 (0.35)	--
P-value	< 0.001 ¹	--	< 0.001 ¹	--	< 0.001	--

¹ Statistically significantly superior compared to placebo at the 0.05 level with multiplicity adjustment.

LS Mean: Least Squares Mean estimated from a mixed model for repeated measures analysis of covariance;
SD: Standard Deviation; SE: Standard Error.

² Mean % Reduction is a descriptive statistic and not from the mixed model.

Results of the co-primary endpoint for change from baseline to weeks 4 and 12 in mean severity of moderate to severe VMS per 24 hours from SKYLIGHT 1 and 2 and from pooled studies are shown in Table 3.

Table 3. Mean baseline and change from baseline to weeks 4 and 12 for mean severity of moderate to severe VMS per 24 hours

Parameter	SKYLIGHT 1		SKYLIGHT 2		Pooled studies (SKYLIGHT 1 and 2)	
	Fezolinetant 45 mg (n=174)	Placebo (n=175)	Fezolinetant 45 mg (n=167)	Placebo (n=167)	Fezolinetant 45 mg (n=341)	Placebo (n=342)
Baseline						
Mean (SD)	2.40 (0.35)	2.43 (0.35)	2.41 (0.34)	2.41 (0.32)	2.40 (0.35)	2.42 (0.34)
Change from baseline to week 4						
LS Mean (SE)	-0.46 (0.04)	-0.27 (0.04)	-0.61 (0.05)	-0.32 (0.05)	-0.53 (0.03)	-0.30 (0.03)
Difference vs Placebo (SE)	-0.19 (0.06)	--	-0.29 (0.06)	--	-0.24 (0.04)	--
P-value	0.002 ¹	--	< 0.001 ¹	--	< 0.001	--
Change from baseline to week 12						
LS Mean (SE)	-0.57 (0.05)	-0.37 (0.05)	-0.77 (0.06)	-0.48 (0.06)	-0.67 (0.04)	-0.42 (0.04)
Difference vs Placebo (SE)	-0.20 (0.08)	--	-0.29 (0.08)	--	-0.24 (0.06)	--
P-value	0.007 ¹	--	< 0.001 ¹	--	< 0.001	--

¹ Statistically significantly superior compared to placebo at the 0.05 level with multiplicity adjustment.

LS Mean: Least Squares Mean estimated from a mixed model for repeated measures analysis of covariance;
SD: Standard Deviation; SE: Standard Error.

Safety: Endometrial safety

In the long-term safety data (SKYLIGHT 1, 2, and 4), endometrial safety of fezolinetant 45 mg was assessed by transvaginal ultrasound and endometrial biopsies (304 women had baseline and post-baseline endometrial biopsies during 52 weeks of treatment).

Endometrial biopsy assessments did not identify an increased risk of endometrial hyperplasia or malignancy according to pre-specified criteria for endometrial safety. Transvaginal ultrasound did not reveal increased endometrial thickness.

5.2 Pharmacokinetic properties

In healthy women, fezolinetant C_{max} and AUC increased proportionally with doses between 20 and 60 mg once daily.

After once-a-day dosing, steady-state plasma concentrations of fezolinetant were generally reached by day 2, with minimal fezolinetant accumulation. The pharmacokinetics of fezolinetant do not change over time.

Absorption

Fezolinetant C_{max} is usually achieved at 1 to 4 hours post-dose. No clinically significant differences in fezolinetant pharmacokinetics were observed following administration with a high-calorie, high-fat meal. Veozza may be administered with or without food (see section 4.2).

Distribution

The mean apparent volume of distribution (V_z/F) of fezolinetant is 189 l. The plasma protein binding of fezolinetant is low (51%). The distribution of fezolinetant into red blood cells is almost equal to plasma.

Biotransformation

Fezolinetant is primarily metabolised by CYP1A2 to yield oxidised major metabolite ES259564. ES259564 is approximately 20-fold less potent against human NK3 receptor. The metabolite-to-parent ratio ranges from 0.7 to 1.8.

Elimination

The apparent clearance at steady-state of fezolinetant is 10.8 l/h. Following oral administration, fezolinetant is mainly eliminated in urine (76.9%) and to a lesser extent in faeces (14.7%). In urine, a mean of 1.1% of the administered fezolinetant dose was excreted unchanged and 61.7% of the administered dose was excreted as ES259564. The effective half-life ($t_{1/2}$) of fezolinetant is 9.6 hours in women with VMS.

Special populations

Effects of age, race, body weight, and menopause status

There are no clinically relevant effects on age (18 to 65 years), race (Black, Asian, Other), body weight (42 to 126 kg), or menopause status (pre-, post-menopause) on the pharmacokinetics of fezolinetant.

Hepatic impairment

Following single-dose administration of 30 mg fezolinetant in women with Child-Pugh Class A (mild) chronic hepatic impairment, mean fezolinetant C_{max} increased by 1.2-fold and AUC_{inf} increased by 1.6-fold, relative to women with normal hepatic function. In women with Child-Pugh Class B (moderate) chronic hepatic impairment, mean fezolinetant C_{max} decreased by 15% and AUC_{inf} increased by 2-fold. The C_{max} of ES259564 decreased in both mild and moderate chronic hepatic impairment groups while AUC_{inf} and AUC_{last} slightly increased less than 1.2-fold.

Fezolinetant has not been studied in individuals with Child-Pugh Class C (severe) chronic hepatic impairment.

Renal impairment

Following single-dose administration of 30 mg fezolinetant, there was no clinically relevant effect on fezolinetant exposure (C_{max} and AUC) in women with mild (eGFR 60 to less than 90 ml/min/1.73 m²) to severe (eGFR less than 30 ml/min/1.73 m²) renal impairment. The AUC of ES259564 was not changed in women with mild renal impairment but increased approximately 1.7- to 4.8-fold in moderate (eGFR 30 to less than 60 ml/min/1.73 m²) and severe renal impairment. Veozta is not recommended for use in women with severe renal impairment or with end-stage renal disease because of lack of long-term safety data in this population.

Fezolinetant has not been studied in individuals with end-stage renal disease (eGFR less than 15 ml/min/1.73 m²).

5.3 Preclinical safety data

Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

Repeated dose toxicity

Repeated administration of fezolinetant to rats and monkeys showed the effects consistent with the primary pharmacological action (oestrous cycle disruptions, the lack of ovarian activity, decreased uterine and/or ovarian weight, uterine atrophy). These effects were observed at high exposure levels (> 10-fold of the anticipated clinical exposure at the human therapeutic dose of 45 mg). Furthermore, in rats, secondary effects were seen on the liver and thyroid which are considered to be an adaptive response to the enzyme induction and in the absence of functional impairment and accompanying necrotic changes were considered non-adverse. The finding of thyroid follicular cell hyperplasia is considered secondary to the liver enzyme induction due to the increased thyroid hormone metabolism, resulting in the positive feedback to the pituitary for the stimulation of thyroid stimulating hormone production and increased thyroid activity. It is generally accepted that rodents are more sensitive to this type of liver-mediated thyroid toxicity than humans, thus these findings are not expected to be clinically relevant.

In monkeys, thrombocytopenia, sometimes associated with haemorrhagic episodes and regenerative anaemia, was seen following repeated administration at high dose levels (> 60-fold of human exposure at the human therapeutic dose).

Genotoxicity

Fezolinetant and its major metabolite ES259564 showed no genotoxic potential in the *in vitro* bacterial reverse mutation test, *in vitro* chromosomal aberration test, and *in vivo* micronucleus test.

Carcinogenicity

An increase in the incidence of thyroid follicular cell adenoma was noted in a 2-year rat carcinogenicity study (186-fold of human exposure at the human therapeutic dose). The increase is considered to be a rat specific effect secondary to the induction of hepatocyte metabolic enzymes and does not constitute a clinical carcinogenic risk.

Additionally, increased incidence of thymomas, which slightly exceeded the historical control range, was observed in both species. However, these findings were only noted at exposure levels significantly in excess (> 50-fold) of the clinical exposure at the human therapeutic dose, and therefore are not expected to be relevant to humans.

Reproductive and developmental toxicity

Fezolinetant had no effect on female fertility or early embryonic development in the rat study at exposure levels of 143-fold of human exposure at the human therapeutic dose.

In embryo-foetal development toxicity studies, embryo-lethality was noted at the exposure levels of 128- and 174-fold at the human therapeutic dose in rats and rabbits, respectively. Rabbits also showed increased late resorption and reduced foetal weight at the exposure levels of 28-fold at the human therapeutic dose. Fezolinetant did not show teratogenic potential in either rats or rabbits. In the pre- and post-natal development study in rats, increased dose-responsive total litter loss/abortions was observed at the exposure levels of 36-fold of the anticipated clinical exposure at the maximum recommended human dose, while reduced sexual maturation in male progeny was seen at the 204-fold exposure levels at the maximum recommended human dose.

Following administration of radiolabelled fezolinetant to lactating rats, the radioactivity concentration in milk was higher than that in the plasma at all time points, indicating excretion of fezolinetant and/or its metabolites in the breast milk.

Environmental Risk Assessment (ERA)

Environmental risk assessment studies have shown that fezolinetant may pose a risk to the aquatic environment (see section 6.6).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core tablet

Mannitol (E421)
Hydroxypropyl cellulose (E463)
Low-substituted hydroxypropyl cellulose (E463a)
Microcrystalline cellulose (E460)
Magnesium stearate (E470b)

Film coating

Hypromellose (E464)
Talc (E553b)
Macrogol (E1521)
Titanium dioxide (E171)
Iron oxide red (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

Alu-Alu blister of 10 tablets. PA/Aluminium/PVC/Aluminium unit dose blisters in cartons.

Pack sizes: Box of 10, 30, and 100 tablets.

6.6 Special precautions for disposal

This medicinal product may pose a risk to the aquatic environment (see section 5.3).

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Manufactured by

Astellas Pharma Inc. Yaizu Technology Center
Shizuoka, Japan

or

Bushu Pharmaceuticals Ltd. Misato Factory
Saitama, Japan

Imported by

Astellas Pharma (Thailand) Co., Ltd.
Bangkok, Thailand

8. MARKETING AUTHORISATION NUMBER

1C 38/67 (NC)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19 November 2024

Date of latest renewal:

10. DATE OF REVISION OF THE TEXT

January 2025